EXAMINER'S NOTES

Access DB# 152886
153405

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Rebecca Clark Examiner #: 69824 Date:

Art Unit: 1614 Phone Number 30 [illegible] Serial Number: 10/602303

Mail Box and Bldg/Room Location: 3C70 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of invention:

Inventors (please provide full names): Bharat Aggarwal

Earliest Priority Filing Date: 6/24/2003

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please provide structures of compounds of claim 44 search them + curcumin to treat multiple myeloma.
Search inventor's own work.
Search in Cancerlit, Medline + other DB's as appropriate

Thank you
Rebecca

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STAFF USE ONLY Type of Search Vendors and cost where applicable

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=> d his ful

     FILE 'REGISTRY' ENTERED AT 10:42:10 ON 16 MAY 2005
L1             7 SEA ABB=ON  (VINCRISTINE OR BCNU OR MELPHALAN OR CYCLOPHOSPHAMI
                 DE OR ADRIAMYCIN OR PREDNISONE OR DEXAMETHASONE)/CN
L2             1 SEA ABB=ON  CURCUMIN/CN

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L3            83 SEA ABB=ON  (L1 OR VINCRISTINE OR BCNU OR MELPHALAN OR
                 CYCLOPHOSPHAMIDE OR ADRIAMYCIN OR PREDNISONE OR DEXAMETHASONE)
                 AND (L2 OR ?CURCUMIN?)
L4             7 SEA ABB=ON  L3 AND ?MULTIPLE?(W)?MYELOMA?  7 cits from CA Plus
                 D AU 1-7

     FILE 'MEDLINE, CANCERLIT, BIOSIS, EMBASE, JAPIO, JICST-EPLUS' ENTERED AT
     11:03:05 ON 16 MAY 2005
L5            14 SEA ABB=ON  L4
L6             8 DUP REMOV L5 (6 DUPLICATES REMOVED)  8 cits from other dbs
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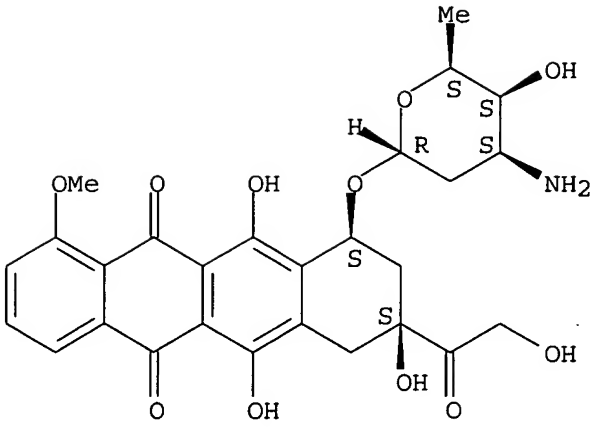
Compounds

=> d l1

L1 ANSWER 1 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 25316-40-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, hydrochloride, (8S,10S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, hydrochloride, (8S-cis)-
CN Adriamycin, hydrochloride (8CI)
OTHER NAMES:
CN ADM hydrochloride
CN ADR
CN Adriablastina CS
CN Adriacin
CN **Adriamycin**
CN Adriblastin
CN Adriblastina
CN Adriblastina RD
CN DOX HCl
CN Doxorubicin hydrochloride
CN FI 106
CN FI 6804
CN Hydroxydaunorubicin hydrochloride
CN Lipodox
FS STEREOSEARCH
MF C27 H29 N O11 . Cl H
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DIOGENES, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSPATENTS, IPA, MRCK*, MSDS-OHS, NIOSHTIC, PATDPASPC, PROMT, PROUSDDR, PS, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
CRN (23214-92-8)

Absolute stereochemistry.



● HCl

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4562 REFERENCES IN FILE CA (1907 TO DATE)
240 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4571 REFERENCES IN FILE CAPLUS (1907 TO DATE)

ED Entered STN: 16 Nov 1984

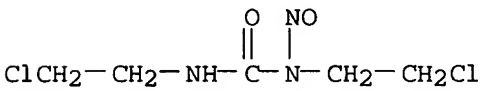
L1 ANSWER 2 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 154-93-8 REGISTRY
ED Entered STN: 16 Nov 1984
CN Urea, N,N'-bis(2-chloroethyl)-N-nitroso- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Urea, 1,3-bis(2-chloroethyl)-1-nitroso- (8CI)
OTHER NAMES:
CN 1,3-Bis(β-chloroethyl)-1-nitrosourea
CN 1,3-Bis(2-chlorethyl)-1-nitrosourea
CN 1,3-Bis(2-chloroethyl)-1-nitrosourea
CN **BCNU**
CN Becenun
CN BiCNU
CN Carmubris
CN Carmustin
CN Carmustine
CN DTI 015
CN FDA 0345
CN Gliadel
CN N,N'-Bis(2-chloroethyl)-N-nitrosourea
CN Nitrumon
CN NSC 409962
CN SK 27702
CN SRI 1720
FS 3D CONCORD
MF C5 H9 Cl2 N3 O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT,

CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HODOC*, IFICDB, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Other Sources: EINECS**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)



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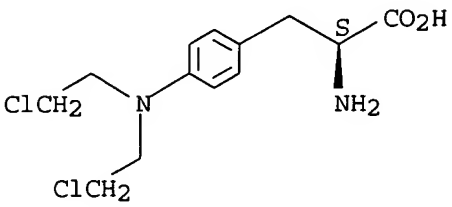
38 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2603 REFERENCES IN FILE CAPLUS (1907 TO DATE)
23 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

ED Entered STN: 16 Nov 1984

L1 ANSWER 3 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 148-82-3 REGISTRY
ED Entered STN: 16 Nov 1984
CN L-Phenylalanine, 4-[bis(2-chloroethyl)amino]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Alanine, 3-[p-[bis(2-chloroethyl)amino]phenyl]-, L- (8CI)
OTHER NAMES:
CN 3025CB
CN Alanine nitrogen mustard
CN Alkeran
CN CB 3025
CN L-PAM
CN L-Phenylalanine mustard
CN L-Phenylalanine mustard hydrochloride
CN L-Sarcolysin
CN L-Sarcolysine
CN L-Sarkolysin
CN Levofalan
CN Levofolan
CN Levopholan
CN Melfalan
CN **Melphalan**
CN NSC 241286
CN NSC 8806
CN Phenylalanine mustard
CN Sarcoclorin
FS STEREOSEARCH
DR 8057-25-8
MF C13 H18 Cl2 N2 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VETU

(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



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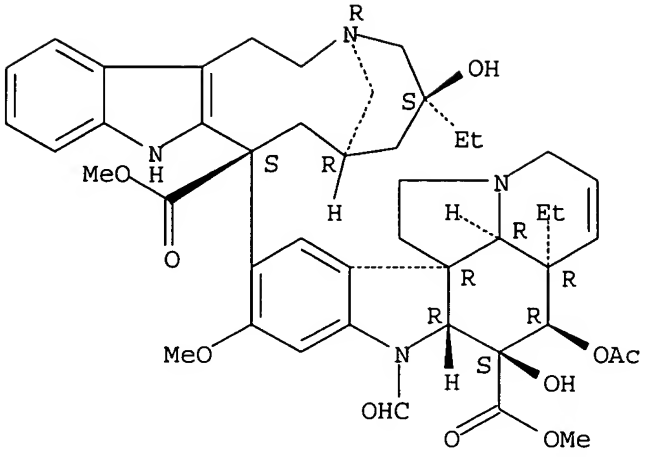
173 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3121 REFERENCES IN FILE CAPLUS (1907 TO DATE)
21 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
ED Entered STN: 16 Nov 1984

L1 ANSWER 4 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 57-22-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN Vincaleukoblastine, 22-oxo- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Indolizino[8,1-cd]carbazole, vincaleukoblastine deriv.
CN 2H-3,7-Methanoazacycloundecino[5,4-b]indole, vincaleukoblastine deriv.
CN Leurocristine (7CI, 8CI)
OTHER NAMES:
CN (+)-Vincristine
CN 22-Oxovincaleukoblastine
CN LCR
CN Leucristine
CN OncoTCS
CN VCR
CN Vincristin
CN **Vincristine**
CN Vinkristin
FS STEREOSEARCH
DR 28379-27-3
MF C46 H56 N4 O10
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PHAR, PROMT, PROUSDDR, PS, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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122 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5948 REFERENCES IN FILE CAPLUS (1907 TO DATE)
8 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

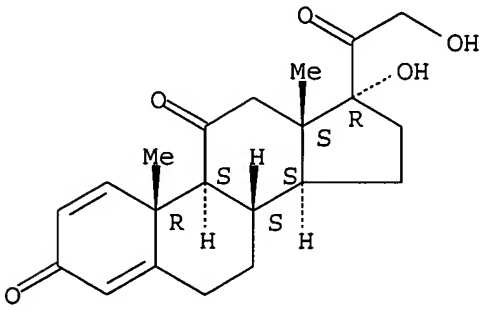
ED Entered STN: 16 Nov 1984

L1 ANSWER 5 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 53-03-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN Pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy- (8CI, 9CI) (CA INDEX NAME)

OTHER NAMES:
CN Δ-Cortisone
CN Δ1-Cortisone
CN Δ1-Dehydrocortisone
CN 1,2-Dehydrocortisone
CN 1,4-Pregnadiene-17α,21-diol-3,11,20-trione
CN 1-Dehydrocortisone
CN 17,21-Dihydroxypregn-1,4-diene-3,11,20-trione
CN 17,21-Dihydroxypregna-1,4-diene-3,11,20-trione
CN 17α,21-Dihydroxy-1,4-pregnadiene-3,11,20-trione
CN Adasone
CN Ancortone
CN Apo-Prednisone
CN Bicortone
CN Cartancyl
CN Colisone
CN Cordrol
CN Cortan
CN Cortidelt
CN Dacorten
CN Dacortin
CN Decortancyl
CN Decortin
CN Decortisyl
CN Dehydrocortisone
CN Dekortin

CN Delcortin
CN Dellacort
CN Dellacort A
CN Delta E
CN Delta-Cortelan
CN Delta-Dome
CN Deltacortene
CN Deltacortisone
CN Deltacortone
CN Deltasone
CN Deltison
CN Deltisona
CN Deltisone
CN Deltra
CN Di-Adreson
CN Drazone
CN Econosone
CN Encorton
CN Encortone
CN Enkorton
CN Fernisone
CN Hostacortin
CN Liquid Pred
CN Me-Korti
CN Metacortandracin
CN **Prednisone**
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
FS STEREOSEARCH
DR 68-59-7
MF C21 H26 O5
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PIRA, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



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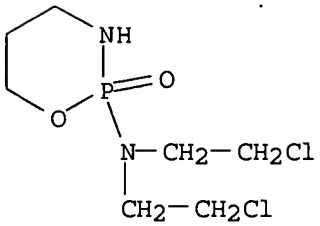
54 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5056 REFERENCES IN FILE CAPLUS (1907 TO DATE)
6 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
ED Entered STN: 16 Nov 1984

L1 ANSWER 6 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 50-18-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN 2H-1,3,2-Oxazaphosphorin-2-amine, N,N-bis(2-chloroethyl)tetrahydro-, 2-oxide (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2H-1,3,2-Oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide (6CI, 8CI)
OTHER NAMES:
CN (±)-Cyclophosphamide
CN (RS)-Cyclophosphamide
CN 2-[Bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorin 2-oxide
CN Asta B 518
CN B 518
CN Bis(2-chloroethyl)phosphoramide cyclic propanolamide ester
CN CB 4564
CN Clafen
CN Claphene
CN CP
CN CPA
CN CTX
CN CY
CN Cycloblastin
CN Cyclophosphamid
CN **Cyclophosphamide**
CN Cyclophosphamidum
CN Cyclophosphan
CN Cyclophosphane
CN Cyclostin
CN Cytophosphan
CN Cytoxan
CN Endoxan
CN Endoxan R
CN Endoxan-Asta
CN Endoxana
CN Endoxanal
CN Endoxane
CN Enduxan
CN Genoxal
CN Hexadrin
CN Mitoxan
CN N,N-Bis(β-chloroethyl)-N',O-trimethylenephosphoric acid ester diamide
CN N,N-Bis(2-chloroethyl)-N',O-propylenephosphoric acid ester diamide
CN NCI C04900
CN Neosar
CN Neosar (antineoplastic)
CN NSC 26271
CN Procytox
CN Semdoxan
CN Sendoxan
CN Senduxan
CN SK 20501

CN Zyklophosphamid
FS 3D CONCORD
DR 60007-95-6, 75526-90-8
MF C7 H15 Cl2 N2 O2 P
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PATDPASPC, PHAR, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

13479 REFERENCES IN FILE CA (1907 TO DATE)
218 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
13505 REFERENCES IN FILE CAPLUS (1907 TO DATE)
256 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
ED Entered STN: 16 Nov 1984

L1 ANSWER 7 OF 7 REGISTRY COPYRIGHT 2005 ACS on STN
RN 50-02-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11β,16α)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1-Dehydro-16α-methyl-9α-fluorohydrocortisone
CN 16α-Methyl-9α-fluoro-Δ1-hydrocortisone
CN 16α-Methyl-9α-fluoro-1,4-pregnadiene-11β,17α,21-triol-3,20-dione
CN 16α-Methyl-9α-fluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione
CN 16α-Methyl-9α-fluoroprednisolone
CN 9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione
CN 9α-Fluoro-11β,17α,21-trihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione
CN 9α-Fluoro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione
CN 9α-Fluoro-16α-methyl-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione
CN 9α-Fluoro-16α-methylprednisolone
CN Adexone
CN Aeroseb-Dex

CN Aphtasolon
CN Aphthasolone
CN Azium
CN Calonat
CN Corsone
CN Cortisumman
CN Decacort
CN Decaderm
CN Decadron
CN Decadron A
CN Decalix
CN Decasone
CN Dekacort
CN Delipos
CN Deltafluorene
CN Dergramin
CN Deronil
CN Desadrene
CN Desameton
CN Deseronil
CN Dexa-Cortidelt
CN Dexa-Mamallet
CN Dexa-Scheroson
CN Dexa-sine
CN Dexacort
CN Dexacortal
CN Dexacortin
CN Dexadeltone
CN Dexafarma
CN Dexalona
CN Dexaltin
CN Dexameth
CN **Dexamethasone**
CN Dexamethasone alcohol
CN Dexamonozon
CN Dexapolcort
CN Dexapos
CN Dexaprol
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
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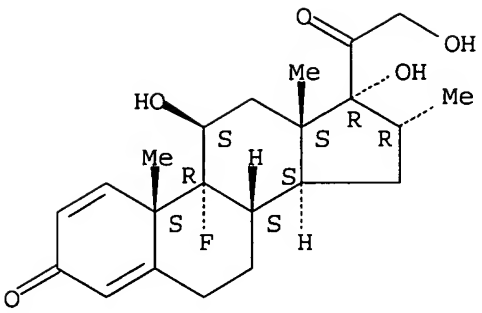
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

22723 REFERENCES IN FILE CA (1907 TO DATE)
295 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
22759 REFERENCES IN FILE CAPLUS (1907 TO DATE)
186 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
ED Entered STN: 16 Nov 1984

=> d l2

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 458-37-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1,6-Heptadiene-3,5-dione, 1,7-bis(4-hydroxy-3-methoxyphenyl)-, (1E,6E)-
(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,6-Heptadiene-3,5-dione, 1,7-bis(4-hydroxy-3-methoxyphenyl)-, (E,E)-
(8CI)
CN **Curcumin (6CI)**
OTHER NAMES:
CN (E,E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione
CN C Yellow 15
CN C.I. 75300
CN C.I. Natural Yellow 3
CN Curcuma
CN Curcumin I
CN Curcumine
CN Diferuloylmethane
CN E 100
CN E 100 (dye)
CN Haidr
CN Halad
CN Haldar
CN Halud
CN Indian Saffron
CN Kacha Haldi
CN Merita Earth
CN Natural Yellow 3
CN NSC 32982
CN San-Ei Curcumine AL
CN San-Ei Gen Curcumine AL
CN Souchet
CN Terra Merita

CN trans,trans-Curcumin
CN Turmeric
CN Turmeric (dye)
CN Turmeric yellow
CN Ukon
CN Ukon (dye)
CN Yellow Ginger
CN Yellow Root
CN Yo-Kin
FS STEREOSEARCH
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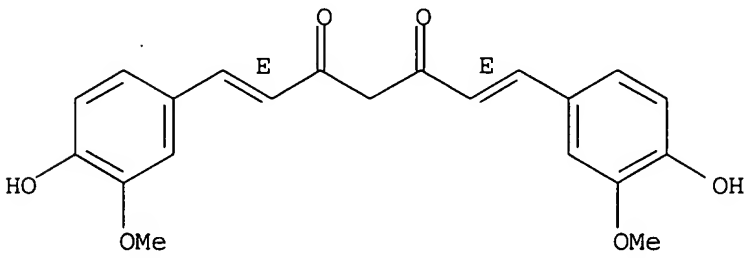
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSRESEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PIRA, PROMT, PROUSDDR, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2080 REFERENCES IN FILE CA (1907 TO DATE)
110 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2091 REFERENCES IN FILE CAPLUS (1907 TO DATE)
21 REFERENCES IN FILE CAOLD (PRIOR TO 1967)
ED Entered STN: 16 Nov 1984

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=> d que stat l4
L1             7 SEA FILE=REGISTRY ABB=ON  (VINCRISTINE OR BCNU OR MELPHALAN OR
                 CYCLOPHOSPHAMIDE OR ADRIAMYCIN OR PREDNISONE OR DEXAMETHASONE)/
                 CN
L2             1 SEA FILE=REGISTRY ABB=ON  CURCUMIN/CN
L3            83 SEA FILE=HCAPLUS ABB=ON  (L1 OR VINCRISTINE OR BCNU OR
                 MELPHALAN OR CYCLOPHOSPHAMIDE OR ADRIAMYCIN OR PREDNISONE OR
                 DEXAMETHASONE) AND (L2 OR ?CURCUMIN?)
L4             7 SEA FILE=HCAPLUS ABB=ON  L3 AND ?MULTIPLE?(W)?MYELOMA?

L4   ANSWER 1 OF 7  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:185396  HCAPLUS
DOCUMENT NUMBER:          142:254582
TITLE:                    Curcuminoids as selective inhibitors of
                          STAT-3 activation and uses in treating cancer or
                          precancer
INVENTOR(S):              Aggarwal, Bharat B.
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 31 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     US 2005049299         A1    20050303    US 2004-925814          20040825
     WO 2005020908         A2    20050310    WO 2004-US27578         20040825
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
             SN, TD, TG
PRIORITY APPLN. INFO.:                        US 2003-497842P     P  20030826
AB   The present invention provides a method of treating a cancerous or
     pre-cancerous state in an individual in need of such treatment, comprising
     the step of administering a pharmacol. ED of a curcuminoid to
     the individual.  Curcumin inhibited interleukin 6-induced
     proliferation of human multiple myeloma cells.

L4   ANSWER 2 OF 7  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:533970  HCAPLUS
DOCUMENT NUMBER:          141:65088
TITLE:                    Methods and compositions for the prevention or
                          treatment of neoplasia comprising a COX-2 inhibitor in
                          combination with an epidermal growth factor receptor
                          antagonist
INVENTOR(S):              Masferrer, Jaime
PATENT ASSIGNEE(S):       Pharmacia Corporation, USA
SOURCE:                   U.S. Pat. Appl. Publ., 103 pp., Cont.-in-part of U.S.
                          Ser. No. 470,951.
                          CODEN: USXXCO
```

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 21
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004127470	A1	20040701	US 2003-651916	20030829
EP 1522313	A1	20050413	EP 2004-26577	19991222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO, CY				
WO 2005037259	A2	20050428	WO 2004-US27574	20040825
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:		
US 1998-113786P	P	19981223
US 1999-470951	B2	19991222
US 1999-385214	A	19990827
EP 1999-968939	A3	19991222
US 2003-651916	A	20030829

AB The present invention relates to a novel method of preventing and/or treating neoplasia disorders in a subject that is in need of such prevention or treatment by administering to the subject at least one COX-2 inhibitor in combination with an EGF receptor antagonist. Compns., pharmaceutical compns. and kits are also described.

L4 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:342327 HCAPLUS
DOCUMENT NUMBER: 140:368302
TITLE: Nuclear factor-κB and STAT3 are constitutively active in CD138+ cells derived from **multiple myeloma** patients, and suppression of these transcription factors leads to apoptosis
AUTHOR(S): Bharti, Alok C.; Shishodia, Shishir; Reuben, James M.; Weber, Donna; Alexanian, Raymond; Raj-Vadhan, Saroj; Estrov, Zeev; Talpaz, Moshe; Aggarwal, Bharat B.
CORPORATE SOURCE: Departments of Bioimmunotherapy, Hematopathology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Blood (2004), 103(8), 3175-3184
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chemoresistance is a major problem in the treatment of patients with **multiple myeloma** (MM). Because of the central role of the nuclear transcription factors nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3) in chemoresistance, cell survival, and proliferation, we investigated whether MM cells derived from patients express activated NF-κB and STAT3 and if their suppression induces apoptosis. We assayed CD138+ cells from the

bone marrow of 22 MM patients and checked for the activated forms of NF-κB and STAT3 by immunocytochem. We found that MM cells from all the patients expressed the activated forms of NF-κB and STAT3 but to a variable degree (NF-κB: low, 3 of 22; moderate, 5 of 22; or high, 14 of 22; STAT3: none, 1 of 22; low, 3 of 22; moderate, 5 of 22; or high, 14 of 22). Constitutive activation of NF-κB was in some cases also independently confirmed by electrophoretic mobility gel shift assay. In contrast to MM patients, activated forms of NF-κB and STAT3 were absent in cells from healthy individuals. Suppression of NF-κB and STAT3 activation in MM cells by ex vivo treatment with **curcumin** (diferuloylmethane) resulted in a decrease in adhesion to bone marrow stromal cells, cytokine secretion, and in the viability of cells. When compared with **curcumin**, **dexamethasone** was less effective in suppression of NF-κB activation and induction of apoptosis in myeloma cells. Overall, our results indicate that fresh cells from MM patients express constitutively active NF-κB and STAT3, and suppression of these transcription factors inhibits the survival of the cells.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:2635 HCAPLUS
DOCUMENT NUMBER: 140:70995
TITLE: Treatment of human **multiple myeloma** with **curcumin**
INVENTOR(S): Aggarwal, Bharat
PATENT ASSIGNEE(S): Research Development Foundation, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004000229	A2	20031231	WO 2003-US19837	20030624
WO 2004000229	A3	20040304		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2489947	AA	20031231	CA 2003-2489947	20030624
US 2004058021	A1	20040325	US 2003-602303	20030624
EP 1523318	A2	20050420	EP 2003-761285	20030624
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: US 2002-390926P P 20020624
WO 2003-US19837 W 20030624

AB All **multiple myeloma** cell lines examined showed constitutively active IκB kinase (IKK), IκBα phosphorylation and constitutively active NF-κB. **Curcumin**, a chemopreventive agent, suppressed constitutive IκBα

phosphorylation through inhibition of IKK activity and downregulated NF-κB. **Curcumin** also downregulated expression of NF-κB-regulated gene products such as IκBα, Bcl-2, Bcl-xL, cyclin D1, and interleukin-6. Consequently, **curcumin** suppressed **multiple myeloma** cell proliferation and arrested cells at the G1/S phase of the cell cycle. **Curcumin** also induced apoptosis and chemosensitivity to **vincristine.** Overall, the results provide a mol. basis for the treatment of **multiple myeloma** patients with this pharmacol. safe agent.

L4 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:875065 HCAPLUS
DOCUMENT NUMBER: 139:358741
TITLE: Synergistic effects of nuclear transcription factor NF-κB inhibitors and antineoplastic agents for the treatment of tumors and tumor metastases
INVENTOR(S): Aggarwal, Bharat
PATENT ASSIGNEE(S): Research Development Foundation, USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003090681	A2	20031106	WO 2003-US12617	20030424
WO 2003090681	A3	20040826		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2483340	AA	20031106	CA 2003-2483340	20030424
US 2004002499	A1	20040101	US 2003-422292	20030424
EP 1496880	A2	20050119	EP 2003-718509	20030424
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: US 2002-375288P P 20020424
WO 2003-US12617 W 20030424

AB The invention provides methods of inhibiting metastasis of a tumor and methods of treating a tumor using a combination of an inhibitor of the activation of nuclear factor NF-κB and a cancer chemotherapeutic agent. In one embodiment of the invention, combination of **curcumin** and paclitaxel (Taxol) can be used to treat and inhibit metastasis of a breast tumor.

L4 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:790896 HCAPLUS
DOCUMENT NUMBER: 139:390906
TITLE: **Curcumin** (diferuloylmethane) inhibits constitutive and IL-6-inducible STAT3 phosphorylation

in human **multiple myeloma** cells
AUTHOR(S): Bharti, Alok C.; Donato, Nicholas; Aggarwal, Bharat B.
CORPORATE SOURCE: Cytokine Research Section, Department of Bioimmunotherapy, Unit 143, University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Journal of Immunology (2003), 171(7), 3863-3871
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Numerous reports suggest that IL-6 promotes survival and proliferation of **multiple myeloma** (MM) cells through the phosphorylation of a cell signaling protein, STAT3. Thus, agents that suppress STAT3 phosphorylation have potential for the treatment of MM. In the present report, we demonstrate that **curcumin** (diferuloylmethane), a pharmacol. safe agent in humans, inhibited IL-6-induced STAT3 phosphorylation and consequent STAT3 nuclear translocation. **Curcumin** had no effect on STAT5 phosphorylation, but inhibited the IFN-α-induced STAT1 phosphorylation. The constitutive phosphorylation of STAT3 found in certain MM cells was also abrogated by treatment with **curcumin.** **Curcumin**-induced inhibition of STAT3 phosphorylation was reversible. Compared with AG490, a well-characterized Janus kinase 2 inhibitor, **curcumin** was a more rapid (30 min vs 8 h) and more potent (10 μM vs 100 μM) inhibitor of STAT3 phosphorylation. In a similar manner, the dose of **curcumin** completely suppressed proliferation of MM cells; the same dose of AG490 had no effect. In contrast, a cell-permeable STAT3 inhibitor peptide that can inhibit the STAT3 phosphorylation mediated by Src blocked the constitutive phosphorylation of STAT3 and also suppressed the growth of myeloma cells. TNF-α and lymphotoxin also induced the proliferation of MM cells, but through a mechanism independent of STAT3 phosphorylation. In addition, **dexamethasone**-resistant MM cells were found to be sensitive to **curcumin.** Overall, our results demonstrated that **curcumin** was a potent inhibitor of STAT3 phosphorylation, and this plays a role in the suppression of MM proliferation.
REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:90410 HCAPLUS
DOCUMENT NUMBER: 139:30341
TITLE: **Curcumin** (diferuloylmethane) down-regulates the constitutive activation of nuclear factor-κB and IκBα kinase in human **multiple myeloma** cells, leading to suppression of proliferation and induction of apoptosis
AUTHOR(S): Bharti, Alok C.; Donato, Nicholas; Singh, Sujay; Aggarwal, Bharat B.
CORPORATE SOURCE: Cytokine Research Section, Department of Bioimmunotherapy, The University of Texas MD Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Blood (2003), 101(3), 1053-1062
CODEN: BLOOAW; ISSN: 0006-4971
Feb 2003
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Because of the central role of the transcription factor nuclear factor-κB (NF-κB) in cell survival and proliferation in human **multiple myeloma** (MM), we explored the possibility of

using it as a target for MM treatment by using **curcumin** (diferuloylmethane), an agent known to have very little or no toxicity in humans. We found that NF-κB was constitutively active in all human MM cell lines examined and that **curcumin**, a chemopreventive agent, down-regulated NF-κB in all cell lines as indicated by electrophoretic mobility gel shift assay and prevented the nuclear retention of p65 as shown by immunocytochem. All MM cell lines showed constitutively active IκB kinase (IKK) and IκBα phosphorylation. **Curcumin** suppressed the constitutive IκBα phosphorylation through the inhibition of IKK activity. **Curcumin** also down-regulated the expression of NF-κB-regulated gene products, including IκBα, Bcl-2, Bcl-xL, cyclin D1, and interleukin-6. This led to the suppression of proliferation and arrest of cells at the G1/S phase of the cell cycle. Suppression of NF-κB complex by IKKγ/NF-κB essential modulator-binding domain peptide also suppressed the proliferation of MM cells. **Curcumin** also activated caspase-7 and caspase-9 and induced polyadenosine-5'-diphosphate-ribose polymerase (PARP) cleavage. **Curcumin**-induced down-regulation of NF-κB, a factor that has been implicated in chemoresistance, also induced chemosensitivity to **vincristine** and **melphalan.** Overall, our results indicate that **curcumin** down-regulates NF-κB in human MM cells, leading to the suppression of proliferation and induction of apoptosis, thus providing the mol. basis for the treatment of MM patients with this pharmacol. safe agent.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d que stat l6
L1             7 SEA FILE=REGISTRY ABB=ON  (VINCRISTINE OR BCNU OR MELPHALAN OR
                 CYCLOPHOSPHAMIDE OR ADRIAMYCIN OR PREDNISONE OR DEXAMETHASONE)/
                 CN
L2             1 SEA FILE=REGISTRY ABB=ON  CURCUMIN/CN
L3            83 SEA FILE=HCAPLUS ABB=ON  (L1 OR VINCRISTINE OR BCNU OR
                 MELPHALAN OR CYCLOPHOSPHAMIDE OR ADRIAMYCIN OR PREDNISONE OR
                 DEXAMETHASONE) AND (L2 OR ?CURCUMIN?)
L4             7 SEA FILE=HCAPLUS ABB=ON  L3 AND ?MULTIPLE?(W)?MYELOMA?
L5            14 SEA L4
L6             8 DUP REMOV L5 (6 DUPLICATES REMOVED)

=> d ibib abs l6 1-8

L6   ANSWER 1 OF 8     MEDLINE on STN                    DUPLICATE 1
ACCESSION NUMBER:   2004203663     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 15070700
TITLE:              Nuclear factor-kappaB and STAT3 are constitutively active
                    in CD138+ cells derived from multiple
                    myeloma patients, and suppression of these
                    transcription factors leads to apoptosis.
AUTHOR:             Bharti Alok C; Shishodia Shishir; Reuben James M; Weber
                    Donna; Alexanian Raymond; Raj-Vadhan Saroj; Estrov Zeev;
                    Talpaz Moshe; Aggarwal Bharat B
CORPORATE SOURCE:   Department of Bioimmunotherapy, The University of Texas M.
                    D. Anderson Cancer Center, Houston 77030, USA.
SOURCE:             Blood, (2004 Apr 15) 103 (8) 3175-84.  Electronic
                    Publication: 2003-12-18.
                    Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:        200405
ENTRY DATE:         Entered STN: 20040423
                    Last Updated on STN: 20040528
                    Entered Medline: 20040527
AB   Chemoresistance is a major problem in the treatment of patients with
     multiple myeloma (MM).  Because of the central role of
     the nuclear transcription factors nuclear factor-kappaB (NF-kappaB) and
     signal transducer and activator of transcription 3 (STAT3) in
     chemoresistance, cell survival, and proliferation, we investigated whether
     MM cells derived from patients express activated NF-kappaB and STAT3 and
     if their suppression induces apoptosis.  We assayed CD138+ cells from the
     bone marrow of 22 MM patients and checked for the activated forms of
     NF-kappaB and STAT3 by immunocytochemistry.  We found that MM cells from
     all the patients expressed the activated forms of NF-kappaB and STAT3 but
     to a variable degree (NF-kappaB: low, 3 of 22; moderate, 5 of 22; or high,
     14 of 22; STAT3: none, 1 of 22; low, 3 of 22; moderate, 5 of 22; or high,
     14 of 22).  Constitutive activation of NF-kappaB was in some cases also
     independently confirmed by electrophoretic mobility gel shift assay.  In
     contrast to MM patients, activated forms of NF-kappaB and STAT3 were
     absent in cells from healthy individuals.  Suppression of NF-kappaB and
     STAT3 activation in MM cells by ex vivo treatment with curcumin
     (diferuloylmethane) resulted in a decrease in adhesion to bone marrow
     stromal cells, cytokine secretion, and in the viability of cells.  When
     compared with curcumin, dexamethasone was less
     effective in suppression of NF-kappaB activation and induction of
     apoptosis in myeloma cells.  Overall, our results indicate that fresh
```

cells from MM patients express constitutively active NF-kappaB and STAT3, and suppression of these transcription factors inhibits the survival of the cells.

L6 ANSWER 2 OF 8 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004455097 EMBASE
TITLE: Apoptosis of **multiple myeloma.**
AUTHOR: Oancea M.; Mani A.; Hussein M.A.; Almasan A.
CORPORATE SOURCE: Dr. A. Almasan, Depts. Cancer Biol. Radiat. Oncol., NB40, Cleveland Clinic Foundation, Cleveland, OH 44195, United States. almasaa@ccf.org
SOURCE: International Journal of Hematology, (2004) Vol. 80, No. 3, pp. 224-231.
Refs: 76
ISSN: 0925-5710 CODEN: IJHEEY
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20041112
Last Updated on STN: 20041112

AB **Multiple myeloma** (MM) is a malignancy of terminally differentiated plasma cells. MM cells localize to the bone marrow, where cell adhesion-mediated autocrine or paracrine activation of various cytokines, such as interleukin 6, insulin-like growth factor 1, and interferon α, results in their accumulation mainly because of loss of critical apoptotic controls. Resistance to apoptosis, a genetically regulated cell death process, may play a critical role in both pathogenesis and resistance to treatment of MM. Abnormalities in regulation and execution of apoptosis can contribute to tumor initiation, progression, as well as to tumor resistance to various therapeutic agents. Apoptosis is executed via 2 main pathways that lead to activation of caspases: the death receptor (extrinsic) pathway and the mitochondrial (intrinsic) pathway. Ionizing radiation and chemotherapeutic agents act primarily through the intrinsic pathway, in which mitochondria play the central role. Various therapeutic modalities that are effective in MM modulate levels of the proapoptotic and antiapoptotic Bcl-2 family of proteins and of inhibitors of apoptosis, expression of which is primarily regulated by p53, nuclear factor κB, and STAT (signal transducers and activators of transcription) factors. This review focuses on the key concepts and some of the most recent studies of signaling pathways regulated in MM and summarizes what is known about the clinical role of these pathways. .COPYRGT. 2004 The Japanese Society of Hematology.

L6 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003441010 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14500688
TITLE: **Curcumin** (diferuloylmethane) inhibits constitutive and IL-6-inducible STAT3 phosphorylation in human **multiple myeloma** cells.
AUTHOR: Bharti Alok C; Donato Nicholas; Aggarwal Bharat B
CORPORATE SOURCE: Cytokine Research Section, Department of Bioimmunotherapy, Unit 143, University of Texas M. D. Anderson Cancer Center,

Houston, TX 77030, USA.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2003 Oct 1) 171 (7) 3863-71.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20030923
Last Updated on STN: 20040108
Entered Medline: 20040107

AB Numerous reports suggest that IL-6 promotes survival and proliferation of **multiple myeloma** (MM) cells through the phosphorylation of a cell signaling protein, STAT3. Thus, agents that suppress STAT3 phosphorylation have potential for the treatment of MM. In the present report, we demonstrate that **curcumin** (diferuloylmethane), a pharmacologically safe agent in humans, inhibited IL-6-induced STAT3 phosphorylation and consequent STAT3 nuclear translocation. **Curcumin** had no effect on STAT5 phosphorylation, but inhibited the IFN-alpha-induced STAT1 phosphorylation. The constitutive phosphorylation of STAT3 found in certain MM cells was also abrogated by treatment with **curcumin. Curcumin**-induced inhibition of STAT3 phosphorylation was reversible. Compared with AG490, a well-characterized Janus kinase 2 inhibitor, **curcumin** was a more rapid (30 min vs 8 h) and more potent (10 micro M vs 100 micro M) inhibitor of STAT3 phosphorylation. In a similar manner, the dose of **curcumin** completely suppressed proliferation of MM cells; the same dose of AG490 had no effect. In contrast, a cell-permeable STAT3 inhibitor peptide that can inhibit the STAT3 phosphorylation mediated by Src blocked the constitutive phosphorylation of STAT3 and also suppressed the growth of myeloma cells. TNF-alpha and lymphotoxin also induced the proliferation of MM cells, but through a mechanism independent of STAT3 phosphorylation. In addition, **dexamethasone**-resistant MM cells were found to be sensitive to **curcumin.** Overall, our results demonstrated that **curcumin** was a potent inhibitor of STAT3 phosphorylation, and this plays a role in the suppression of MM proliferation.

L6 ANSWER 4 OF 8 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003022721 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12393461
TITLE: **Curcumin** (diferuloylmethane) down-regulates the constitutive activation of nuclear factor-kappa B and IkappaBalpha kinase in human **multiple myeloma** cells, leading to suppression of proliferation and induction of apoptosis.
AUTHOR: Bharti Alok C; Donato Nicholas; Singh Sujay; Aggarwal Bharat B
CORPORATE SOURCE: Cytokine Research Section, Department of Bioimmunotherapy, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
SOURCE: Blood, (2003 Feb 1) 101 (3) 1053-62. Electronic Publication: 2002-09-05.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200304

ENTRY DATE: Entered STN: 20030117
Last Updated on STN: 20030422
Entered Medline: 20030421

AB Because of the central role of the transcription factor nuclear factor-kappaB (NF-kappaB) in cell survival and proliferation in human **multiple myeloma** (MM), we explored the possibility of using it as a target for MM treatment by using **curcumin** (diferuloylmethane), an agent known to have very little or no toxicity in humans. We found that NF-kappaB was constitutively active in all human MM cell lines examined and that **curcumin**, a chemopreventive agent, down-regulated NF-kappaB in all cell lines as indicated by electrophoretic mobility gel shift assay and prevented the nuclear retention of p65 as shown by immunocytochemistry. All MM cell lines showed consitutively active IkappaB kinase (IKK) and IkappaBalpha phosphorylation. **Curcumin** suppressed the constitutive IkappaBalpha phosphorylation through the inhibition of IKK activity. **Curcumin** also down-regulated the expression of NF-kappaB-regulated gene products, including IkappaBalpha, Bcl-2, Bcl-x(L), cyclin D1, and interleukin-6. This led to the suppression of proliferation and arrest of cells at the G(1)/S phase of the cell cycle. Suppression of NF-kappaB complex by IKKgamma/NF-kappaB essential modulator-binding domain peptide also suppressed the proliferation of MM cells. **Curcumin** also activated caspase-7 and caspase-9 and induced polyadenosine-5'-diphosphate-ribose polymerase (PARP) cleavage. **Curcumin**-induced down-regulation of NF-kappaB, a factor that has been implicated in chemoresistance, also induced chemosensitivity to **vincristine** and **melphalan.** Overall, our results indicate that **curcumin** down-regulates NF-kappaB in human MM cells, leading to the suppression of proliferation and induction of apoptosis, thus providing the molecular basis for the treatment of MM patients with this pharmacologically safe agent.

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ACCESSION NUMBER: 2004054433 EMBASE
TITLE: Nuclear factor-κB as a predictor of treatment response in breast cancer.
AUTHOR: Garg A.K.; Hortobagyi G.N.; Aggarwal B.B.; Sahin A.A.; Buchholz T.A.
CORPORATE SOURCE: Dr. T.A. Buchholz, Department of Radiation Oncology, Univ. TX M. D. Anderson Cancer Ctr., Unit 97, 1515 Holcolmbe Blvd., Houston, TX 77030, United States. tbuchhol@mdanderson.org
SOURCE: Current Opinion in Oncology, (2003) Vol. 15, No. 6, pp. 405-411.
Refs: 111
ISSN: 1040-8746 CODEN: CUOOE8
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 014 Radiology
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040304
Last Updated on STN: 20040304

AB Purpose of review: To examine the links of nuclear factor-κB (NF-κB) to treatment-induced signaling in breast cancer and to

propose further studies to elucidate the role of NF-κB in breast cancer response to chemotherapy and radiation. Recent findings: The authors' group and others have investigated the clinical relevance of ubiquitously expressed NF-κB in breast cancer. Possibly through its effects on apoptosis, NF-κB has been implicated in tumor resistance to chemotherapy and radiation in many types of tumors. Furthermore, both in vitro and in vivo studies have shown that targeted inhibition of NF-κB can sensitize tumor cells to chemotherapy and radiation. Summary: The molecular mechanisms involved in chemotherapy-induced and radiation-induced cell death in breast cancer are not fully known, nor are the mechanisms of treatment resistance. NF-κB is a transcription factor for a number of genes involved in tumor progression and resistance to systemic therapies and is a major regulator of the apoptotic pathway. Gaining further insights into molecular factors such as NF-κB as biomarkers for treatment response may help clinicians predict treatment outcome and lead to the development of targeted therapeutics.

L6 ANSWER 6 OF 8 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:184577 BIOSIS
DOCUMENT NUMBER: PREV200400181675
TITLE: Differential effects of the combination of **curcumin** with conventional chemotherapeutic agents on human **multiple myeloma** cells.
AUTHOR(S): Zavrski, Ivana [Reprint Author]; Eucker, Jan [Reprint Author]; Heider, Ulrike [Reprint Author]; Jakob, Christian [Reprint Author]; Fleissner, Claudia [Reprint Author]; Possinger, Kurt [Reprint Author]; Sezer, Orhan [Reprint Author]
CORPORATE SOURCE: Hematology and Oncology, Universitaetsklinikum Charite, Berlin, Germany
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 376b. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
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AB **Curcumin**, a polyphenol found in the spice turmeric, is the major yellow pigment used in curries. **Curcumin** was shown to induce apoptosis in cancer cells and was thought to have a chemopreventive effect. Inactivation of NF-kappaB, inhibition of c-Jun N-terminal kinase, downregulation of cell surface adhesion molecules, cyclin D1, bcl-2 and MMP-9, inhibition of protein kinase C and activation of caspases were the most common effects due to **curcumin** in tumor cell lines. The aim of this study was to evaluate, whether the addition of **curcumin** to widely used cytostatic drugs in the treatment of **multiple myeloma**, e.g. **melphalan**, doxorubicin and **dexamethasone**, could enhance or inhibit the induction of apoptosis and could inhibit growth in human **multiple myeloma** cells. Using the MTT-assay, we found that **curcumin** inhibits the growth of freshly isolated human bone marrow myeloma cells and myeloma cell lines in a dose dependent manner (10-100 muM). The addition of **curcumin** to 1muM **melphalan** could slightly increase the apoptosis in all examined cell lines. When **curcumin** was added to doxorubicin (100, 250 or 1000 nM), we

observed a reduced growth inhibition in U266 and LP-1 cells in comparison to doxorubicin alone, and an enhanced growth inhibition in RPMI-S. In all examined cell lines, the addition of 10 muM **curcumin** to 1 or 5 muM **dexamethasone** failed to enhance apoptosis. Interestingly, in freshly isolated myeloma cells from bone marrow aspirates from patients. 100 and 250 nM doxorubicin reduced the pro-apoptotic effect of **curcumin.** In conclusion, our data show that **curcumin** inhibits myeloma cell growth and induces apoptosis when applied alone. The addition of **curcumin** to **melphalan** increased the pro-apoptotic effect of **curcumin**, but **curcumin** antagonized doxorubicin and **dexamethasone.** The inhibition of doxorubicin-induced apoptosis may be related to the inhibition of reactive oxygen species and c-Jun N-terminal kinase by **curcumin.** Addition of **curcumin** to other chemotherapeutic agents should occur with caution.

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ACCESSION NUMBER: 2003215854 EMBASE
TITLE: Rationale for the treatment of solid tumors with the proteasome inhibitor bortezomib.
AUTHOR: Cusack Jr. J.C.
CORPORATE SOURCE: Dr. J.C. Cusack Jr., Harvard Medical School, Massachusetts General Hospital, Boston, MA 02114, United States. jcusack@partners.org
SOURCE: Cancer Treatment Reviews, (2003) Vol. 29, No. SUPPL. 1, pp. 21-31.
Refs: 82
ISSN: 0305-7372 CODEN: CTREDJ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
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Last Updated on STN: 20030612

AB Given its role in cellular metabolism, the proteasome could prove to be a critical target that can be exploited in treating cancer. In preclinical studies, several mechanisms for bortezomib's activity in **multiple myeloma** cells have been identified (e.g., NF-κB inhibition); antitumor activity with bortezomib has been seen in myeloma patients, thereby supporting the validity of the preclinical work. Similar mechanisms may be in play in solid tumors, and cell culture and xenograft data suggest bortezomib may be active in a wide range of tumor types. One promising possibility is the use of bortezomib for the treatment of chemoresistant tumors. Chemoresistance can be caused by a number of cellular factors; NF-κB is a prominent instigator of chemoresistance, and proteasome inhibition was an effective means of preventing NF-κB activation in myeloma and several solid tumor laboratory studies. However, the inhibition of NF-κB may not be the only mechanism for antitumor activity. This review explores the use of proteasome inhibitors to subvert intrinsic resistance mechanisms, disrupt inducible chemoresistance, or augment the mechanisms of action of standard chemotherapeutics. Thus, in addition to providing another target for anticancer treatment, proteasome inhibition may also provide a means to treat refractory tumors. .COPYRGT. 2003 Elsevier Science Ltd. All rights reserved.

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ACCESSION NUMBER: 2004048450 EMBASE
TITLE: NFκB: Bench to Bedside - Keystone Symposium: 25 February - 3 March 2002, Keystone, CO, USA.
AUTHOR: Amit S.; Ben-Neriah Y.
CORPORATE SOURCE: Y. Ben-Neriah, Lautenberg Center for Immunology, Hebrew University of Jerusalem, Hadassah Medical School, Jerusalem 91120, Israel. yinon@cc.huji.ac.il
SOURCE: IDrugs, (2002) Vol. 5, No. 4, pp. 331-335.
ISSN: 1369-7056 CODEN: IDRUFN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 029 Clinical Biochemistry
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037 Drug Literature Index
030 Pharmacology
038 Adverse Reactions Titles
014 Radiology
039 Pharmacy
005 General Pathology and Pathological Anatomy
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